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Welders are at increased risk for invasive pneumococcal disease

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SUMMARY

Background: Welders are at increased risk of pulmonary infection and lobar pneumonia, likely due to significant occupational exposure to metal fumes. We hypothesized that welders would be at increased risk for invasive pneumococcal disease (IPD) compared to the general population.
Methods: A retrospective chart review of all patients with IPD in the province of Alberta, Canada (population approx. 3.3 million) was conducted from 2000 to 2004 to study the epidemiology of IPD.
Results: There were 18 cases identified in welders, giving an attack rate of 22.7 cases per 100 000 population per year (95% confidence interval (CI) 12.23–33.23). Compared with an attack rate of 8.7 cases per 100 000 population per year (95% CI 8.10–9.26) for the general adult population between ages 18 and 65 years, there was a 2.7-fold greater incidence of IPD in welders (95% CI 1.67–4.22, $p < 0.001$). There was an increased prevalence of serotypes 4 and 8 compared to the general population. Eight of 18 cases were caused by serotypes in the 7-valent pneumococcal conjugate vaccine, 11 of 18 cases by serotypes in the 13-valent pneumococcal conjugate vaccine, and 18 of 18 cases by serotypes in the 23-valent pneumococcal polysaccharide vaccine. Seventeen patients had bacteremic pneumococcal pneumonia and one had meningitis; one person died due to infection. Fifteen of 18 patients were either current or former smokers, which was a higher rate than the general population adjusted for age and gender (odds ratio 2.976, 95% CI 0.908–9.729, $p = 0.084$).
Conclusions: Welders, particularly those who smoke, are at increased risk of IPD and should be considered for routine administration of the pneumococcal polysaccharide vaccine. Ongoing workplace measures to reduce exposure to metal fumes and promote smoking cessation should be reinforced.

Introduction

Streptococcus pneumoniae is an important cause of community-acquired pneumonia and bacteremia. Invasive pneumococcal disease (IPD) is defined as isolation of *S. pneumoniae* from a normally sterile body site (typically blood or cerebrospinal fluid), and carries with it significant morbidity and mortality. Numerous risk factors for IPD have been identified, which include extremes of age, various medical co-morbidities including congestive heart failure and diabetes mellitus, alcohol abuse, smoking, solid-organ or hematological transplant, and immunosuppression.[1–4] Vaccination of adults with the 23-valent pneumococcal polysaccharide vaccine offers a protective benefit against IPD, and is recommended for adults in high-risk groups.[5,6]

In the context of a large five-year retrospective study of all patients with IPD in the province of Alberta, we sought to clarify the relationship between occupation and IPD, particularly in 'high-risk' occupations where routine work exposures could predispose individuals to IPD. For the purposes of our study, the occupations considered included welding, farming, day care workers, and electricians.

Methods

Demographics and definitions

The study encompassed the province of Alberta from 2000 to 2004, which at the time of the study was divided into nine health regions. The provincial population was 2 967 755 in 2000 and 3 179 036 in 2004.[7] Cases of IPD were defined as the isolation of *S. pneumoniae* from any normally sterile body site, including blood, cerebrospinal fluid, pleural fluid, biopsy tissue, synovial fluid,

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pericardial fluid, and peritoneal fluid.[8] In Alberta, IPD is considered a notifiable disease reportable to the Provincial Health Office. *S. pneumoniae* isolates recovered from patients with IPD are submitted to the National Centre for Streptococcus (NCS) located in Edmonton, Alberta, for capsular serotyping and antimicrobial resistance profiling for trending analysis. Isolates were submitted to the NCS prospectively from acute diagnostic microbiology laboratories in Alberta during the study period.

To ensure as complete as possible the capture of all patients with IPD in Alberta during the study period, a number of databases were utilized. These included all patients identified by identification of *S. pneumoniae* isolates sent to the NCS, all patients reported to the Provincial Health Office, and all patients captured in both the Calgary Area *S. pneumoniae* Epidemiology Research (CASPER) database (Calgary, AB) and the Community Acquired Pneumonia Study database (Edmonton, AB). All four databases were combined to form the final dataset, and duplicate patients were counted only once. An extensive retrospective chart review of all identified patients was then performed for all identified cases of IPD occurring during the survey period. Current occupations were recorded as self-reported by patients, including whether they were unemployed or retired.

In the laboratory, upon receipt of *S. pneumoniae* isolates, bacteria were stored at −70 °C until serotyping and susceptibility assays were performed. Only one isolate from each IPD case was included in the review unless the isolates were collected one month or more apart in time, or were of a different serotype if less than one month had elapsed between episodes of IPD.

Annual incidence rates for the general population were calculated between 2000 and 2004 using provincial population estimates from Alberta Health and Wellness. Annual occupation-specific incidence rates were calculated between 2000 and 2004 using provincial estimates for various occupations provided by Alberta Employment and Immigration.

The study received approval from the institutional research review committees of all nine health regions in Alberta and also by the University of Alberta and the University of Calgary.

Serotyping of S. pneumoniae isolates

Isolates received at the NCS were confirmed as *S. pneumoniae* based on morphology and optochin susceptibility.[9] Serotyping was performed at the NCS by the Quellung reaction using commercial antisera prepared at the World Health Organization (WHO) Collaborating Center for Reference and Research on Pneumococci, located at the Statens Serum Institut, Copenhagen, Denmark.[10] Strains that failed to type were confirmed as *S. pneumoniae* using Accuprobe™ (Genprobe, San Diego, CA, USA).

Statistical analysis

Incidence rates and serotype prevalence were compared between identified 'high-risk' occupations and the general 'working adult' population between the ages of 18 and 65 years using Fisher's exact test. All statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

Incidence rates of IPD in 'at-risk' occupations vs. general population

A total of 1768 cases of IPD were identified in Alberta between 2000 and 2004 for which laboratory and clinical data were both complete. Of these, 863 cases (48.8%) occurred in 'working-age' patients aged between 18 and 65 years, for an overall incidence rate of 8.7 cases per 100 000 population per year (95% confidence interval (CI) 8.10–9.26). Within this group, the incidence rate in males (9.7 cases per 100 000 population per year, 95% CI 8.87–10.60, $p < 0.001$) was slightly higher than the incidence rate in females (7.6 cases per 100 000 population per year, 95% CI 6.84–8.38).

The incidence rates of IPD during the study period for each of four identified 'at-risk' occupations are given in Table 1 and compared with rates of IPD in the 'working-age' general adult population between the ages of 18 and 65 years. A total of 18 patients with IPD (1.02%) were identified during the five-year study period in those who reported their current occupation as welding, for an overall occupation-specific incidence rate of 22.7 cases per 100 000 population per year (95% CI 12.23–33.23). Compared with the remainder of the general adult population between ages 18 and 65 years, welders had a 2.7-fold (95% CI 1.67–4.22; $p < 0.0001$) greater incidence of IPD. All of the affected individuals were male, and in comparison with the remainder of males between ages 18 and 65 years, there was still a 2.4-fold increase (95% CI 1.50–3.81, $p = 0.001$) in the rate of IPD.

Electricians (12.2 cases per 100 000 population per year, 95% CI 12.45–22.04, $p = 0.329$) and day care workers (10.5 cases per 100 000 population per year, 95% CI 3.21–17.70, $p = 0.555$) had an increased rate of IPD compared to the remainder of the working-age population, but neither reached statistical significance. Farmers had a lower rate of IPD (3.1 cases per 100 000 population per year, 95% CI 0.81–5.42, $p = 0.002$) compared to the remainder of the working-age population.

Demographic and clinical characteristics of welders with IPD

Selected demographic and clinical information on the IPD cases in welders is provided in Table 2. All of the involved welders were male, with a median age of 39 years. Thirteen (72%) were current smokers and two (11%) were former smokers. Six reported significant alcohol use and four reported the use of illicit drugs. Compared with males aged between 18 and 65 years with IPD, the affected welders had a greater tendency to be either current or former smokers (15/18 (83%) vs. 294/469 (63%), odds ratio (OR) 2.976, 95% CI 0.908–9.729, $p = 0.084$). There was no significant difference in rates of alcohol use between affected welders and males aged between 18 and 65 years with IPD (159/487, 33%). There was no pattern of medical co-morbidities identified, although one patient had a history of recurrent upper respiratory infection and 'metal fume fever', as described by the patient. There was no geographic clustering of cases.

Table 1
Rates of invasive pneumococcal disease in identified 'at-risk' occupations, 2000–2004.

Occupation	IPD cases 2000–2004	Number employed 2000–2004, in person- years	Incidence rate/100 000/year (95% CI)	Odds ratio (95% CI) compared to general population	*p*-Value[a]
Welder	18	79 200	22.7 (12.23–33.23)	2.653 (1.670–4.215)	<0.001
Electrician	6	49 000	12.2 (2.45–22.04)	1.414 (0.646–3.093)	0.329
Farmer	7	224 700	3.1 (0.81–5.42)	0.354 (0.171–0.732)	0.002
Day care worker	8	76 500	10.5 (3.21–17.70)	1.207 (0.610–2.389)	0.555

CI, confidence interval.
[a] Two-tailed Fisher's exact test.

Table 2
Baseline characteristics of welders with invasive pneumococcal disease ($N = 18$).

Characteristic	
Median age (range in years)	39 (21–60)
Gender (male/female)	18/0
Smoker (current/former/never)	13/2/3
Significant alcohol use	6
Illicit drug use	4
Medical co-morbidities	
Hypertension	2
Hepatitis C	3
Recurrent upper respiratory infection	1
Clinical presentation	
Pneumonia	16
Seizures/? encephalitis	1
Fever NYD	1
Source of isolate	
Bacteremia	17
Cerebrospinal fluid	1
Hospitalization	
Admitted	16
ER only	1
Outpatient only	1
ICU admission	4
Mechanical ventilation	3
Tube thoracostomy	4
Mean time in hospital (days ± SD)	8.63 ± 11.37
Hospitalization ≥7 days	11
Hospitalization between 7.1 and 28 days	4
Hospitalization >28 daysH	1
Range (days)	1–43
Mean time in ICU (days ± SD)	9.5 ± 9.68
Range (days)	1–21
In-hospital mortality	1

Results are *n*, unless otherwise stated.
NYD, not yet diagnosed; ER, emergency room; ICU, intensive care unit; SD, standard deviation.

Seventeen patients had pneumococcal bacteremia and one patient had meningitis. All had radiographic changes (predominantly lobar infiltrates) consistent with community-acquired pneumonia. Sixteen patients required hospital admission and of these, four required intensive care unit (ICU) admission. Three patients required mechanical ventilation and four patients required tube thoracostomy for either empyema or pleural effusion. There was a single death which occurred in the patient with meningitis, who was admitted to an ICU and who died one day after admission to hospital. For all patients admitted to hospital (including the patient who died), the average length of stay was 8.63 days (range 1–43 days), with 10 being discharged in one week or less. For those admitted to an ICU (including the patient who died), the average length of ICU admission was 9.5 days (range 1–21 days).

S. pneumoniae serotypes of isolates from welders with IPD

There was an increased prevalence of serotypes 4 (6/18 (33%) vs. 121/827 (15%), OR 2.917, 95% CI 1.113–7.660, $p = 0.004$) and 8 (3/18 (17%) vs. 69/827 (9%), OR 2.197, 95% CI 0.666–7.289, $p = 0.193$) compared with the working-age population. Two cases were caused by serotype 7F, and one case was caused by each of serotypes 1, 9N, 9 V, 12F, 14, 22F, and 33F. Eight cases (44%) were caused by serotypes covered by the 7-valent conjugate vaccine (PCV7) and 11 cases (61%) caused by serotypes covered by the 13-valent conjugate vaccine (PCV13). All 18 cases were caused by serotypes covered by the 23-valent polysaccharide vaccine (PPV23).

Discussion

A significant excess of lobar pneumonia in welders from England and Wales in comparison with what would be expected from age-specific rates in the general population was described by Coggon et al.[11] This excess risk was not observed in those above retirement age, lending support to the existence of a reversible occupation-specific risk factor. The chemical properties of welding fumes are complex, and the most common elemental constituents include iron, chromium, and nickel. Animal studies have demonstrated that exposure to stainless steel welding fumes, which contain large amounts of chromium and nickel, promotes lung inflammation and injury.[12] Chronic exposure to metal fumes blunts the inflammatory response of lung tissue against inhaled particulate matter, which may predispose to the development of respiratory infection.[13] Specifically, chromium is most likely the primary constituent responsible for suppression of lung defense mechanisms.[14] Exposure to metal fumes has been shown to predispose to pneumonia, with a particular association between lobar pneumonia and recent exposure to ferrous fumes.[15] Increased rates of pneumonia have been identified in other occupations with exposure to metal fumes, such as furnace men and foundry workers.[11]

During our five-year retrospective analysis (2000–2004), we identified 18 cases of IPD in welders in the province of Alberta, a 2.7-fold increased incidence of IPD in this occupational group compared to the general adult working population between ages 18 and 65 years. Seventeen of 18 had invasive pneumococcal bacteremia and all patients had clinical symptoms and radiographic changes consistent with pneumonia (predominantly lobar pneumonia). Clinical outcomes were favorable in most of these patients, but four required ICU admission and there was one death directly attributed to IPD in a patient who developed pneumococcal meningitis and who also had clinical findings compatible with pneumonia.

Eleven of 18 cases were caused by pneumococcal serotypes covered by PCV13 and all cases involved serotypes covered by PPV23. We did not identify a significant increase in IPD attack rates in other 'at-risk' occupations such as electricians, farmers, and day-care workers.

Cigarette smoking is a strong independent risk factor for IPD in immunocompetent, non-elderly adults. In a 1995 population-based surveillance study performed in Dallas County, Texas, smoking was associated with a 2.6-fold increase (95% CI 1.9–3.5) for those between the ages of 24 and 64 years.[16] In a population-based case–control study published in 2000, for those between 18 and 64 years of age with IPD, there was a 4.1-fold increase in risk (95% CI 2.4–7.3) for those who actively smoked. There was also evidence of a dose–response curve with respect to both total duration of smoking and number of daily cigarettes smoked.[2]

Fifteen of the 18 affected welders were either current or former smokers (83%), which was higher than the remainder of males of working-age in our study (OR 2.976, 95% CI 0.908–9.729, $p = 0.084$), though not statistically significant. The increased rates of IPD in welders seen in our study may at least be partially conferred due to smoking, but the added risk from occupational exposure remains real. Baseline demographics on all welders in the province (such as age and smoking rates) during the study period were not available, which precludes further analysis to determine the relative impact of occupational exposure and smoking on IPD risk in this population. For comparison, rates of smoking were also increased in affected electricians (5/6) compared to males of working age, but not in farmers (2/7). All affected day care workers were female, and rates of smoking in this group (4/8) were not increased compared to the remainder of working-age females.

Currently, PPV23 is recommended for all adults aged ≥65 years and in younger patients with a wide variety of medical conditions that increase the risk of IPD.[9,10] Canadian guidelines for the administration of PPV23 would not be applicable to the significant

majority of welders. Our report links a specific occupation to an increased risk of IPD and is a logical extension of the previous literature reporting increased lobar pneumonia in welders and those exposed to metal fumes, most of which were presumably caused by *S. pneumoniae*. Consideration should be given to the routine administration of PPV23 in all welders, and the profession as a whole should be made aware of the increased risk of pneumonia and invasive disease. Ongoing workplace measures to reduce exposure to metal fumes should be encouraged.

There are limitations with our study. We only captured patients with a positive isolate, and it is possible that cases of IPD were missed if cultures were not done or if they were negative (e.g., if drawn after the administration of antibiotics). We relied on documentation of occupation on the patient charts, and it is possible that cases were missed because occupation was not documented. Our study thus provides a minimal estimate of the risk of IPD in different occupations and the actual risk may be higher. A higher proportion of affected welders in our study were either current or former smokers when compared to the affected general population adjusted for age and gender, which suggests that some of the increased risk of IPD in welders seen in our study may be attributable to smoking rather than occupational exposure. Although the presence of co-morbidities amongst affected welders was minimal, there could have been other confounding factors not accounted for in this study.

In summary, our data demonstrate that welders are at increased risk of IPD, particularly those who smoke. Consideration should be given to pneumococcal vaccination in all members of this occupation, and the importance of smoking cessation should be reinforced. Those in the profession, especially those who smoke, should be made aware of the increased risk of pneumonia and invasive disease and the potential benefits of vaccination. Workplace measures to reduce exposure to metal fumes and encourage smoking cessation should be encouraged and actively monitored.

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Conflict of interest: TJM, JDK, and GJT have received compensation from Wyeth for consulting and speaking about pneumococcal vaccination, and financial support from Wyeth for performing epidemiologic analyses of cases of invasive pneumococcal disease in the province of Alberta.

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